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Prevention and Treatment of Neonatal Herpes Simplex Virus Infection

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Abstract

Herpes simplex virus (HSV), a member of the Herpesviridae family, is a well-known cause of infections including genital herpes and herpes labialis in the adolescent and adult population. Transmission of HSV infection to an infant during the first 4–6 weeks of life can lead to devastating disease with the potential for poor outcomes. Early diagnosis is imperative when evaluating neonatal HSV infection in order to prevent further disease progression, neurological complications, and even death. In the past 4 decades, significant advancements have been made in the diagnosis, treatment, and prevention of neonatal HSV infection, but there remains room for improvement as efforts continue to reduce the burden of disease caused by this infection.

Keywords

Herpes simplex virus; acyclovir; neonatal herpes; antiviral therapy; mother-to-child transmission

Introduction

Herpes simplex virus (HSV) infection occurs infrequently in neonates despite the ubiquitous nature of the virus in adults. Neonatal HSV disease occurs in about 1500 infants a year in the United States (Pinninti and Kimberlin, 2013), but recent studies suggest an increasing incidence over the last several years (Mahant et al., 2019). Both HSV-1 and HSV-2 can cause neonatal HSV disease, and to improve overall outcome in infants diagnosed with neonatal HSV disease, early diagnosis and initiation of treatment is imperative. Early initiation of therapy prevents further disease progression (Kimberlin et al., 2001b). Therefore, clinicians should have a low threshold to evaluate an infant for the disease.

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Authors' Note

We are honored to contribute this work to Antiviral Research's symposium dedicated to the memory of Mark N. Prichard, PhD. Mark was an exceptionally gifted and generous colleague who made everyone around him better. I (SHJ) had the privilege of working side-by-side with Mark in our laboratory for over a decade, during which time his tremendous mentorship and friendship shaped me in ways I still cannot fully comprehend. As we strive to honor his memory and carry on his legacy, our hope is that the work to which he was so dedicated will continue to impact lives throughout the world.

Over the last 40 years, advances in diagnostic testing and antiviral therapy have aided in improving outcomes and survival of neonates diagnosed with the disease. This article will review the classification of neonatal HSV disease, the current diagnostic approach, the recommended antiviral treatment regimen, and approaches in preventing transmission of the disease to neonates.

Description of the pathogen

HSV is an enveloped, double-stranded DNA virus that belongs to the Herpesviridae family and the alpha herpesviruses subgroup (Whitley and Roizman, 2001). Members of the alpha herpesviruses subgroup have a unique capability of establishing latency in sensory neural ganglia after primary infection and can reactivate periodically to cause either a recurrent localized infection or subclinical viral shedding (Whitley and Baines, 2018). HSV is composed of 4 parts: a viral double-stranded DNA genome with a long and short component, icosahedral capsid comprised of 162 capsomeres, a protein layer surrounding the capsid often referred to as the tegument, and an envelope comprised of 11 glycoproteins which are used for attachment and penetration of the virus into host cells (Whitley and Roizman, 2001). For diagnostic purposes, HSV-1 and HSV-2 can be differentiated by type-specific antibodies to glycoproteins G-1 and G-2, respectively (James and Kimberlin, 2015b; Pinninti and Kimberlin, 2013).

Transmission

Transmission of HSV from mother to infant has been linked to several risk factors. These risk factors include the mother's type of infection (first-episode primary, first-episode non-primary, or recurrent infection, as defined below), maternal serologic status (when available), HSV typing of genital lesion, isolation of HSV at delivery, vaginal versus cesarean delivery, duration of rupture of membranes, and use of fetal scalp electrodes (Pinninti and Kimberlin, 2013). Commercially available HSV serologic assays have improved over the last decade making the differentiation between HSV-1 and HSV-2 immunoglobulins possible. This allows for serologic results and viral lesion HSV type to be compared, and thus, determine maternal infection type. Women with first-episode primary infection lack antibodies to both HSV-1 and HSV-2, and these mothers are at the greatest risk of transmitting HSV to their infant. Mothers with first-episode non-primary infection have antibodies for either HSV-1 or HSV-2 but newly acquire the other HSV type. Women with recurrent infection already have antibodies to the virus type being shed. Women with first-episode non-primary infection and recurrent infection have a lower risk of transmitting the virus as they are able to pass HSV-1 or HSV-2 IgG antibodies transplacentally to their infant to provide some protection (Brown et al., 2003). IgM immunoglobulins are not used in determining maternal infection type. Although maternal serologies can aid in determining the infants at greatest risk of infection, they are often not known unless a mother presents with an active genital lesion at time of delivery, and most infants diagnosed with neonatal HSV disease are born to mothers who are asymptomatically shedding the virus.

Classification and clinical presentation of neonatal HSV disease

By definition, neonatal HSV disease occurs in infants less than 42 days old, with a majority of cases presenting in the first four weeks of life (Curfman et al., 2016). Infants acquire the

virus either during intrauterine (rare), peripartum (85% of cases), or postpartum (10% of cases) time periods (Corey and Wald, 2009). Intrauterine infections are quite rare and the diagnosis is usually made at birth as a result of array of findings indicative of intrauterine infection, including skin abnormalities (scarring, hypo/hyperpigmented lesions, active skin vesicles), cutis aplasia, microcephaly, chorioretinitis, and/or retinal dysplasia (Hutto et al., 1987).

There are three classifications of HSV disease in neonates: (1) skin, eye, and mouth (SEM), (2) central nervous system (CNS), and (3) disseminated disease. SEM disease is characterized by skin lesions or other localized involvement of the mouth or eye. Infants with CNS disease have been characterized to have focal (temporal region) or generalized seizures, irritability, poor feeding, and/or temperature instability with or without skin lesions. Disseminated disease is diagnosed based on multiple organ involvement including lungs, adrenal glands, liver, and/or central nervous system (Pinninti and Kimberlin, 2013). Most infants with disseminated disease do not develop a vesicular rash. The majority of infants presenting with neonatal HSV disease are classified as having SEM disease (45%), followed by CNS disease (30%), and then disseminated disease (20%) (Kimberlin, 2004). Infants with SEM or disseminated disease typically present at 10–12 days of life whereas those with CNS disease typically present later, around 16–19 days of life. Disease classification is clinically important because it is predictive of neurodevelopmental outcome and mortality, with CNS and disseminated disease being of greater risk (Kimberlin et al., 2001b).

Diagnosis of neonatal HSV disease

All infants undergoing evaluation for neonatal HSV disease should have: ‘surface swabs’ obtained from the eye, nasopharynx, mouth, and rectum and sent for culture and PCR; culture and PCR obtained from any concerning mucocutaneous lesion; blood HSV PCR; serum alanine aminotransferase (ALT); and a lumbar puncture performed to obtain cerebrospinal fluid (CSF) for HSV PCR testing. Cultures of vesicular lesions and ‘surface swabs’ continue to be the gold standard for diagnostics, but PCR is quickly becoming the more favorable option because of its faster turnaround time and increased sensitivity (Pinninti and Kimberlin, 2013). However, studies have yet to prove superiority of PCR over culture and there remains the risk of false positive PCR results. The implementation of PCR on CSF samples has greatly impacted the diagnosis of CNS disease, making brain biopsies no longer routinely necessary (Kimberlin et al., 1996; Lakeman and Whitley, 1995). If CSF HSV DNA PCR is negative but an infant’s clinical presentation is concerning for neonatal HSV CNS disease, a diagnosis of neonatal HSV CNS disease should still be considered since false negatives are possible.

Serum HSV PCR has also been useful in the early detection of neonatal HSV disease, especially in patients without cutaneous manifestations, and may at times be the only positive diagnostic test (Cantey et al., 2015; Cantey et al., 2012). However, a negative serum HSV PCR must not be used to rule out the diagnosis. A positive serum HSV PCR is more commonly seen with more invasive disease manifestations (CNS and disseminated) but has been noted to be negative in invasive disease cases as well (Lyons et al., 2018; Melvin et

al., 2015). The results of all the diagnostic tests aid in classifying the disease into SEM, CNS, or disseminated disease, which determines the minimum duration of treatment. All infants diagnosed with neonatal HSV disease should be evaluated by ophthalmology and have neuroimaging performed even if no central nervous system involvement is documented (Kabani and Kimberlin, 2018).

Treatment of neonatal HSV disease

The treatment of neonatal HSV disease has significantly improved over the last 40 years with the advancements in antiviral therapy. Prior to introduction of antivirals, 50% of infants with CNS disease and 85% of infants with disseminated disease died (Kimberlin, 2004). Vidarabine was the first antiviral agent recommended in the late 1970s for treatment of neonatal HSV disease (Kimberlin, 2004; Pinninti and Kimberlin, 2013) as previous antiviral agents, idoxuridine and cytarabine, were too toxic for use (Boston Interhospital Virus Study and Study, 1975; Narang, 1982).

In the 1980s, acyclovir, an acyclic guanine nucleoside analog, was licensed for use against herpes virus infections (James and Kimberlin, 2015a; Whitley, 2002), and it quickly became the drug of choice for treatment of neonatal HSV disease due to its more favorable toxicity profile and its ease of administration compared to vidarabine. Acyclovir relies on viral thymidine kinase for its initial phosphorylation step prior to additional phosphorylation by host cellular kinases to form the triphosphate metabolite of acyclovir, which inhibits viral DNA polymerase (Whitley, 2002). At the low dose initially studied (10 mg/kg/dose three times a day), acyclovir did not show therapeutic superiority regarding mortality or morbidity when compared to vidarabine (Whitley et al., 1991). Both vidarabine and low dose acyclovir reduced mortality to 14% in infants with CNS disease and 54% in those with disseminated disease (Kimberlin, 2004). Additional doses of acyclovir were studied to determine if outcomes improved with higher doses; high dose acyclovir (20 mg/kg/dose three times a day) demonstrated a further decrease in mortality for both the CNS and disseminated group to 4% and 30% respectively, thus becoming the standard of care for treatment of neonatal HSV disease (Kimberlin, 2004).

Duration of therapy with intravenous acyclovir is determined by the disease classification. Infants with SEM disease are treated for a total of 14 days with intravenous acyclovir, whereas infants with CNS or disseminated disease are treated with at least 21 days of therapy. All infants with central nervous system involvement require repeat lumbar puncture(s) to assess for clearance of the virus prior to stopping intravenous therapy (James and Kimberlin, 2015b). Initially, infants with CNS disease were only recommended to be treated with 14 days of intravenous acyclovir, but almost half of the patients required longer durations of therapy because of the persistence of the viral DNA in the CSF (Whitley and Baines, 2018). If there is continued detection of viral DNA by HSV PCR around 21 days of therapy, intravenous acyclovir should be extended an additional week and a repeat lumbar puncture should be performed to obtain CSF for HSV PCR testing (Pinninti and Kimberlin, 2013). In the setting of persistently positive CSF HSV PCR results beyond 21 days of therapy, intravenous acyclovir should be discontinued only after a negative CSF HSV PCR is achieved.

All infants on intravenous acyclovir should be monitored for neutropenia and evidence of renal toxicity, with twice weekly complete blood count with differential and daily creatinine levels. Decreasing the dose of intravenous acyclovir or administering granulocyte-colony stimulating factor (G-CSF) are two possible approaches a clinician may take if an infant develops severe neutropenia (absolute neutrophil count reaches <500 cells/ μL) while receiving intravenous acyclovir (Kimberlin et al., 2001a).

After completion of the recommended 14- or 21-day treatment course with intravenous acyclovir determined by patient's classification of neonatal HSV disease, patients are transitioned to oral acyclovir (300 mg/m^2/dose three times a day) to complete a 6-month course of suppressive therapy. The initiation of suppressive therapy demonstrated a reduction in recurrent skin lesions in those with cutaneous manifestations and improvement in the neurologic development in those with CNS involvement (Kimberlin et al., 2011). Infants should continue to be monitored for signs of neutropenia while on oral acyclovir; the risk of reversible nephrotoxicity is more apparent with intravenous acyclovir than with oral acyclovir, therefore, close monitoring is not necessary. Infants should have a complete blood count with differential performed on the 2^{nd} and 4^{th} week of administration of oral acyclovir and then monthly thereafter to monitor for neutropenia. Infants with an absolute neutrophil count ≤ 500 cells/μL should have their oral acyclovir held until their absolute neutrophil count recovers (James and Kimberlin, 2015a). Follow up for these infants should be on a monthly basis to have their dose of oral acyclovir adjusted to account for weight gain as the infant grows.

Currently, acyclovir is the only recommended antiviral agent for treatment of neonatal HSV disease. One study attempted to evaluate the pharmacokinetics of valacyclovir down to one month of age, but recommendations could not be provided as only one dose was studied and those less than 3 months were noted to have decreased clearance (Kimberlin et al., 2010). Several new antiviral agents with activity against HSV are in development, but none have progressed to clinical investigation in infants as of yet (Poole and James, 2018).

Prevention

As a result of the severity of the disease in neonates, measures aimed at preventing transmission have become of great importance. These measures include performing cesarean delivery for mothers with active genital lesions at time of delivery, decreasing contact exposure to persons with active herpes labialis or gingivostomatitis, reducing the use of fetal scalp electrodes, and implementing suppressive therapy in pregnant women with a history of genital herpes (James et al., 2014).

The majority of neonatal HSV infection occurs via perinatal transmission (exposure to the virus during passage through the birth canal), therefore, preventative measures to reduce the risk of transmission to neonates have focused on the perinatal period. Daily suppressive antiviral therapy for women with a history of genital herpes can aid in the reduction of recurrent episodes and subclinical viral shedding, and has been recommended for all pregnant women with recurrent genital herpes starting at 36 weeks gestation (Bulletins, 2007). Although it can reduce the chances of a pregnant woman having an active genital lesion at time of delivery, it does not always prevent asymptomatic shedding so there

is still a risk of transmission from mother to infant. Women presenting with prodromal symptoms (burning or tingling) or active genital lesions at time of delivery should undergo cesarean delivery prior to the rupture of membranes, as recommended by the American College of Obstetricians and Gynecologists (ACOG), in order to lessen the risk of perinatal transmission (Bulletins, 2007). Even if rupture of membranes occurs prior, cesarean delivery should still be performed if active lesions or prodromal symptoms are present. If women have a history of genital herpes but no active lesions at time of delivery, cesarean section is not routinely recommended as the risk outweighs the benefit (James and Kimberlin, 2015b). Although these measures aid in reduction of transmission, a majority of infants are exposed during delivery to asymptomatic mothers who have no prior history of HSV. Thus, providers should have a high degree of suspicion in diagnosing infants regardless of maternal history.

The American Academy of Pediatrics provided a guidance statement on further evaluation of neonates born to mothers with active lesions at the time of delivery in an effort to diagnose infants earlier before disease progression occurs. The guidance statement does not provide any recommendations regarding women with a history of genital herpes but without any active lesions at time of delivery who may be asymptomatically shedding the virus. All genital lesions consistent with HSV disease should be confirmed and typed for HSV-1 or HSV-2. The mother's serologic status should also be evaluated to determine if it is the first-episode primary infection, first-episode non-primary infection, or a recurrent infection (Kimberlin et al., 2013). Knowing whether the infection is first-episode primary infection, first-episode non-primary infection, or recurrent infection aids in determining the risk of transmission to the infant as those with first-episode primary infection are at greater risk of transmitting virus to infant. No recommendations currently exist for screening asymptomatic pregnant women for HSV by serology. Such screening would not likely be of use in predicting infants at high risk of neonatal HSV infection because it cannot reliably identify primary infections (Prober et al., 1988). It is advised, however, that any pregnant woman known or presumed to be negative for HSV should remain abstinent during her third trimester if in a relationship with a known seropositive partner (Bulletins, 2007). Performing viral cultures on pregnant women with a history of HSV disease is also not warranted antepartum as women with asymptomatic viral shedding are at lower risk of transmitting the virus than in those women with primary infection (Arvin et al., 1986; Prober et al., 1988).

In addition to these attempts to interrupt mother-to-child transmission of HSV, efforts are also being made to develop a vaccine that will reduce disease burden by preventing primary infection in women prior to their child-bearing years. Several vaccines have been evaluated for their potential use in preventing the acquisition of HSV infections. While some have been able to demonstrate immunogenicity, none have made it to licensure yet (Whitley and Baines, 2018). Nevertheless, HSV vaccine development continues to remain a field of high interest, with several possible vaccine candidates currently being studied (Dropulic et al., 2019).

References:

1. Arvin AM, Hensleigh PA, Prober CG, Au DS, Yasukawa LL, Wittek AE, Palumbo PE, Paryani SG, Yeager AS, 1986. Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery. N Engl J Med 315, 796–800. [PubMed: 3018565]

2. Boston Interhospital Virus Study, G., Study, N.I.-S.C.A.C., 1975. Failure of high dose 5-iodo-2'-deoxyuridine in the therapy of herpes simplex virus encephalitis. Evidence of unacceptable toxicity. N Engl J Med 292, 599–603. [PubMed: 1089874]

3. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L, 2003. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 289, 203–209. [PubMed: 12517231]

4. Bulletins A.C.o.P., 2007. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. No. 82 June 2007. Management of herpes in pregnancy. Obstet Gynecol 109, 1489–1498. [PubMed: 17569194]

5. Cantey JB, Klein AM, Sanchez PJ, 2015. Herpes Simplex Virus DNAemia Preceding Neonatal Disease. J Pediatr 166, 1308–1309. [PubMed: 25720363]

6. Cantey JB, Mejias A, Wallihan R, Doern C, Brock E, Salamon D, Marcon M, Sanchez PJ, 2012. Use of blood polymerase chain reaction testing for diagnosis of herpes simplex virus infection. J Pediatr 161, 357–361. [PubMed: 22608699]

7. Corey L, Wald A, 2009. Maternal and neonatal herpes simplex virus infections. N Engl J Med 361, 1376–1385. [PubMed: 19797284]

8. Curfman AL, Glissmeyer EW, Ahmad FA, Korgenski EK, Blaschke AJ, Byington CL, Miller AS, 2016. Initial Presentation of Neonatal Herpes Simplex Virus Infection. J Pediatr 172, 121–126 e121. [PubMed: 26960921]

9. Dropulic LK, Oestreich MC, Pietz HL, Laing KJ, Hunsberger S, Lumbard K, Garabedian D, Turk SP, Chen A, Hornung RL, Seshadri C, Smith MT, Hosken NA, Phogat S, Chang LJ, Koelle DM, Wang K, Cohen JI, 2019. A Randomized, Double-Blinded, Placebo-Controlled, Phase 1 Study of a Replication-Defective Herpes Simplex Virus (HSV) Type 2 Vaccine, HSV529, in Adults With or Without HSV Infection. J Infect Dis 220, 990–1000. [PubMed: 31058977]

10. Hutto C, Arvin A, Jacobs R, Steele R, Stagno S, Lyrene R, Willett L, Powell D, Andersen R, Werthammer J, et al. , 1987. Intrauterine herpes simplex virus infections. J Pediatr 110, 97–101. [PubMed: 3794894]

11. James SH, Kimberlin DW, 2015a. Neonatal Herpes Simplex Virus Infection. Infect Dis Clin North Am 29, 391–400. [PubMed: 26154662]

12. James SH, Kimberlin DW, 2015b. Neonatal herpes simplex virus infection: epidemiology and treatment. Clin Perinatol 42, 47–59, viii. [PubMed: 25677996]

13. James SH, Sheffield JS, Kimberlin DW, 2014. Mother-to-Child Transmission of Herpes Simplex Virus. J Pediatric Infect Dis Soc 3 Suppl 1, S19–23. [PubMed: 25232472]

14. Kabani N, Kimberlin DW, 2018. Neonatal Herpes Simplex Virus Infection. NeoReviews 19, e89–e96.

15. Kimberlin DW, 2004. Neonatal herpes simplex infection. Clin Microbiol Rev 17, 1–13. [PubMed: 14726453]

16. Kimberlin DW, Baley J, Committee on Infectious D, Committee on F, Newborn, 2013. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics 131, 383–386. [PubMed: 23378604]

17. Kimberlin DW, Jacobs RF, Weller S, van der Walt JS, Heitman CK, Man CY, Bradley JS, 2010. Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. Clin Infect Dis 50, 221–228. [PubMed: 20014952]

18. Kimberlin DW, Lakeman FD, Arvin AM, Prober CG, Corey L, Powell DA, Burchett SK, Jacobs RF, Starr SE, Whitley RJ, 1996. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis 174, 1162–1167. [PubMed: 8940204]

19. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, de Sierra TM, Weller S, Soong SJ, Kiell J, Lakeman FD, Whitley RJ, National Institute of, A., Infectious Diseases Collaborative Antiviral Study, G., 2001a. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 108, 230–238. [PubMed: 11483782]

20. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Frenkel LM, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, de Sierra TM, Soong SJ, Kiell J, Lakeman FD, Whitley RJ, National Institute of A, Infectious Diseases Collaborative Antiviral Study, G., 2001b. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 108, 223–229. [PubMed: 11483781]

21. Kimberlin DW, Whitley RJ, Wan W, Powell DA, Storch G, Ahmed A, Palmer A, Sanchez PJ, Jacobs RF, Bradley JS, Robinson JL, Shelton M, Dennehy PH, Leach C, Rathore M, Abughali N, Wright P, Frenkel LM, Brady RC, Van Dyke R, Weiner LB, Guzman-Cottrill J, McCarthy CA, Griffin J, Jester P, Parker M, Lakeman FD, Kuo H, Lee CH, Cloud GA, National Institute of A, Infectious Diseases Collaborative Antiviral Study, G., 2011. Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med 365, 1284–1292. [PubMed: 21991950]

22. Lakeman FD, Whitley RJ, 1995. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis 171, 857–863. [PubMed: 7706811]

23. Lyons TW, Cruz AT, Freedman SB, Nigrovic LE, Herpes Simplex Virus Study Group of the Pediatric Emergency Medicine Collaborative Research, C., 2018. Accuracy of Herpes Simplex Virus Polymerase Chain Reaction Testing of the Blood for Central Nervous System Herpes Simplex Virus Infections in Infants. J Pediatr 200, 274–276 e271. [PubMed: 29784511]

24. Mahant S, Hall M, Schondelmeyer AC, Berry JG, Kimberlin DW, Shah SS, Pediatric Research in Inpatient Settings, N., the Collaborative Antiviral Study, G., 2019. Neonatal Herpes Simplex Virus Infection Among Medicaid-Enrolled Children: 2009–2015. Pediatrics 143.

25. Melvin AJ, Mohan KM, Schiffer JT, Drolette LM, Magaret A, Corey L, Wald A, 2015. Plasma and cerebrospinal fluid herpes simplex virus levels at diagnosis and outcome of neonatal infection. J Pediatr 166, 827–833. [PubMed: 25491092]

26. Narang HK, 1982. Pathological findings of adenine arabinoside (ARA-A) and cytarabine (ARA-C) in the treatment of herpes simplex encephalitis in rabbit model. Antiviral Res 2, 53–67. [PubMed: 6285819]

27. Pinninti SG, Kimberlin DW, 2013. Neonatal herpes simplex virus infections. Pediatr Clin North Am 60, 351–365. [PubMed: 23481105]

28. Poole CL, James SH, 2018. Antiviral Therapies for Herpesviruses: Current Agents and New Directions. Clin Ther 40, 1282–1298. [PubMed: 30104016]

29. Prober CG, Hensleigh PA, Boucher FD, Yasukawa LL, Au DS, Arvin AM, 1988. Use of routine viral cultures at delivery to identify neonates exposed to herpes simplex virus. N Engl J Med 318, 887–891. [PubMed: 2832756]

30. Whitley R, Arvin A, Prober C, Burchett S, Corey L, Powell D, Plotkin S, Starr S, Alford C, Connor J, et al. , 1991. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med 324, 444–449. [PubMed: 1988829]

31. Whitley R, Baines J, 2018. Clinical management of herpes simplex virus infections: past, present, and future. F1000Res 7.

32. Whitley RJ, 2002. Herpes simplex virus infection. Semin Pediatr Infect Dis 13, 6–11. [PubMed: 12118847]

33. Whitley RJ, Roizman B, 2001. Herpes simplex virus infections. Lancet 357, 1513–1518. [PubMed: 11377626]

Highlights:

1. Diagnosing and initiating treatment early can improve morbidity and mortality of infants with neonatal HSV disease.
2. Acyclovir, an acyclic guanine nucleoside analog, is the only antiviral agent recommended for treatment and for suppressive therapy in neonatal HSV disease.
3. Suppressive therapy with oral acyclovir for 6 months has demonstrated a decrease in recurrences and has improved developmental outcomes.
4. Cesarean sections in women presenting with active genital lesions at time of delivery has reduced the transmission of herpes from mother to infant.
5. The use of suppressive therapy in pregnant females with a history of genital herpes has reduced the chance of having active lesions at time of delivery and decreased periods of subclinical viral shedding.